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Health Effects Assessment for 1,1,2,2-Tetrachloroethane

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HEALTH EFFECTS ASSESSMENT FOR 1,1,2,2-TETRACHLOROETHANE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for 1,1,2,2-tetrachloroethane based on oral exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,1,2,2-tetrachloroethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Chlorinated Ethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-029. NTIS PB 81-117400.

U.S. EPA. 1982a. Revision and update of Hazard profile on 1,1,2,2-tetrachloroethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1982b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of 1,1,2,2-Tetrachloroethane. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Health and Environmental Effects Profile for 1,1,2,2-Tetrachloroethane. Prepared by the Enviornmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards

exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The issue of primary concern is the carcinogenic potential of 1,1,2,2-tetrachloroethane. Human data addressing this issue are not available. Limited *in vitro* mutagenicity data are positive. Only one cancer bioassay has been conducted. In this study 1,1,2,2-tetrachloroethane was not carcinogenic in rats, but was carcinogenic in mice by oral exposure. Exposure resulted in an increased incidence of hepatocellular carcinoma. Using the mouse data, a human q_1^* of 0.20 $(mg/kg/day)^{-1}$ was computed. Data are not available that would allow assessment of the carcinogenic potential of this compound by inhalation exposure.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
ppm	Parts per million
rpm	Revolutions per minute
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,1,2,2-tetrachloroethane (CAS No. 79-34-5) are given in Table 1-1.

The half-life for 1,1,2,2-tetrachloroethane in the atmosphere (Table 1-1) is based on its interaction with OH radicals. Although no estimate of half-life is available, the removal of this compound by wet precipitation may play an important role in removing the compound from air (Callahan et al., 1979). The estimate of half-life for 1,1,2,2-tetrachloroethane in aquatic media is based on the estimated half-life of evaporation of this compound when stirred at 200 rpm in still air at 25°C (Dilling, 1977) and the consideration that, in natural aquatic media containing particulate matter and sediments, an increase in evaporation half-life is expected.

The half-life of this compound in soil could not be located in the available literature. However, by analogy with aquatic media, evaporation is expected to be the predominant loss mechanism from the soil surface. In subsurface soil, in the absence of significant biodegradation (on the basis of lack of biodegradation in aquatic media) (Tabak et al., 1981), the compound is likely to leach from soil to groundwater (Page, 1981).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for 1,1,2,2,-Tetrachloroethane

Properties	Values	Reference
Chemical class:	halogenated aliphatic hydrocarbon	NA
Molecular weight:	167.86	Verschueren, 1983
Vapor pressure:	5 mm Hg at 20°C	Verschueren, 1983
Water solubility:	2900 mg/ℓ at 20°C	Verschueren, 1983
Octanol/water partition coefficient:	245	Banerjee et al., 1980
BCF:	8 for bluegill (Lepomis macrochirus)	U.S. EPA, 1980a
Half-lives in		
Air:	1.6 years	Singh et al., 1981
Water:	>1 hour (estimated)	NA

NA = Not applicable

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Pertinent data regarding the absorption of orally administered 1,1,2,2-tetrachloroethane could not be located in the available literature.

2.2. INHALATION

Lehmann and Hasegawa (1910) administered 9.1 mg/m³ 1,1,2,2-tetrachloroethane by inhalation to one rabbit for a period of 3 hours. During this period, 258.3 mg of the 883.3 mg administered was absorbed.

Human volunteers absorbed 97% of a single 2.5 mg dose of 1,1,2,2-tetrachloroethane vapor (Morgan et al., 1970, 1972). One hour later, 3-6% of the administered dose was exhaled.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the toxicity of orally administered 1,1,2,2-tetrachloroethane could not be located in the available literature.

3.1.2. Inhalation. Schmidt et al. (1972) exposed 105 male rats to 1.94 ppm (13.32 mg/m³) 1,1,2,2-tetrachloroethane vapors for 4 hours/day for 265 days. Multiplying 13.32 mg/m³ by the product of 4/24 hours, 7/7 days and the average inhalation rate for a rat (0.26 m³/day), and then dividing by the average weight of a rat (0.35 kg), the exposure level is adjusted to a dose of 1.65 mg/kg bw/day. Control rats were exposed only to air. Effects associated with exposure to 1,1,2,2-tetrachloroethane included increased white blood cell count, pituitary ACTH and total fat content of the liver, and decreased body weight.

Navrotskiy et al. (1971) exposed unspecified numbers of rabbits to either 0.3, 1.46 or 14.6 ppm (2.06, 10.03 and 100.25 mg/m³) 1,1,2,2-tetrachloroethane for 3-4 hours/day for 7-11 months. At 14.6 ppm, liver and kidney degeneration, "altered" blood chemistry and suppressed hemaglutinin production were observed. Decreased hematocrit, decreased hemoglobin content of red cells, and suppressed hemaglutinin production were observed at 1.46 ppm, while no effects were seen at 0.3 ppm.

Horiuchi et al. (1962) exposed a single monkey to 1000-4000 ppm (13,734-27,468 mg/m³) 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for a total of 190 days. Multiplying 27,468 mg/m³ by the product of 2/24 hours, 6/7 days and the average inhalation rate for a monkey (1.4 m³/day), and then dividing by the average weight of a monkey (3.5 kg), the 4000 ppm exposure level is equivalent to a dose of 756 mg/kg bw/day. These

investigators reported signs of weakness after the seventh exposure, diarrhea and anorexia after the twelfth exposure, and anesthesia after the fifteenth exposure. Other symptoms reported include marked vacuolization of the liver and fluctuations in hematocrit, white blood cell count and red cell hemoglobin content.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic toxicity of orally administered 1,1,2,2-tetrachloroethane could not be located in the available literature.

3.2.2. Inhalation. The effects associated with occupational exposure to 1,1,2,2-tetrachloroethane by inhalation or dermal routes are primarily neurological. Grimm et al. (1914) reported that workers who were exposed to 1,1,2,2-tetrachloroethane in a German aircraft factory experienced pain, tremors, headaches, numbness, excessive perspiration and the sensation of "pins and needles" in the extremities. Women exposed to 1,1,2,2-tetrachloroethane in a factory that produced artificial pearls experienced paralysis of the interosseous muscles of the hands and feet, and paralysis of muscles of the eye and jaw (Leri and Breitel, 1922). Workers in India's bangle industry were exposed to 9-98 ppm 1,1,2,2-tetrachloroethane and had tremors (35%), vertigo (30.5%), headache (26.6%), abdominal pain (23.7%) and anorexia (22.6%) (Lobo-Mendonca, 1963). As summarized in Table 3-1, the percentage of individuals having hand tremors was correlated to the level of exposure to 1,1,2,2-tetrachloroethane in four different plants.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of orally administered 1,1,2,2-tetrachloroethane could not be located in the available literature.

TABLE 3-1

Percentage of Individuals with Hand Tremors with Respect to 1,1,2,2-Tetrachloroethane Exposure in Four Different Factories[a]

Percent	1,1,2,2-Tetrachloroethane[b] (ppm)
50	65 and 98
40	50 and 61
33	40 and 74
14	9 and 17

[a]Source: Lobo-Mendonca, 1963

[b]Values are averages of unspecified numbers of samples

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled 1,1,2,2-tetrachloroethane could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding the interactions of 1,1,2,2-tetrachloroethane with other toxicants could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of ingested 1,1,2,2-tetrachloroethane could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 1,1,2,2-tetrachloroethane could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. An NCI (1978) bioassay reported that 1,1,2,2-tetrachloroethane was carcinogenic in $B6C3F_1$ mice but not in Osborne-Mendel rats. Groups of 50 males and 50 females of each species were exposed to 1,1,2,2-tetrachloroethane in corn oil by gavage for 5 days/week for 78 weeks, and then observed for 12 weeks. No significant increase in any tumor type or total tumors was observed in rats exposed by gavage to 1,1,2,2-tetrachloroethane at TWA doses of 0, 62 and 108 mg/kg or 0, 43 and 76 mg/kg/males and females, respectively. The results in mice are summarized in Table 4-1.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 1,1,2,2-tetrachloroethane could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Brem et al. (1974) reported that 1,1,2,2-tetrachloroethane was mutagenic to histidine-requiring strains of Salmonella typhimurium and preferentially inhibited the growth of a DNA polymerase-deficient strain of Escherichia coli. Callahan et al. (1979) observed mitotic gene conversion in Saccharomyces cerevisiae strain D7.

TABLE 4-1

Incidence of Tumors in Mice Exposed to >90% Pure 1,1,2,2-Tetrachloroethane (in corn oil) by Gavage[a]

Sex	Dose[b] (mg/kg/day)	Duration of Treatment	Duration of Study	Tumor Type	Tumor Incidence (p Value)[c]
M	203	78 weeks	90 weeks	hepatocellular carcinoma	44/49 (p<0.001)
M	101	78 weeks	90 weeks	hepatocellular carcinoma	13/50 (NR)[d]
M	0	78 weeks	91 weeks	hepatocellular carcinoma	1/18 (p<0.001)
F	203	78 weeks	90 weeks	hepatocellular carcinoma	43/47 (p<0.001)
F	101	78 weeks	90 weeks	hepatocellular carcinoma	30/48 (p<0.001)
F	0	78 weeks	91 weeks	hepatocellular carcinoma	0/20 (p<0.001)

[a]Source: NCI, 1978

[b]TWA dose reflecting 5/7 days per week treatment

[c]p levels for the Fisher Exact test and Cochran-Armitage tests are given when <0.05

[d]p = 0.033 when compared with pooled vehicle controls

4.4. WEIGHT OF EVIDENCE

Pertinent data regarding the carcinogenicity of 1,1,2,2-tetrachloroethane in humans could not be located in the available literature. In the NCI (1978) bioassay, the chemical was found to be associated with hepatocellular carcinoma in mice, but the validity of liver tumors in mice as an indicator of the potential of a chemical to cause human cancer is not universally accepted. The evidence, therefore, that 1,1,2,2-tetrachloroethane is an animal carcinogen is best considered to be limited. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) for the overall weight of evidence for human carcinogenicity, 1,1,2,2-tetrachloroethane is most appropriately classified in Group C - Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The OSHA standard for 1,1,2,2-tetrachloroethane in the workplace is 5 ppm (35 mg/m^3) with the designation that dermal exposure may be a significant route of absorption (Code of Federal Regulations, 1981). However, NIOSH (1976) and ACGIH (1983) recommend a TWA of 1 ppm (7 mg/m^3) for occupational exposure to 1,1,2,2-tetrachloroethane. ACGIH (1983) also recommends a STEL of 5 ppm (35 mg/m^3). The ACGIH values were established to prevent "serious intoxication and nervous, hepatic, and gastrointestinal effects" (ACGIH, 1980).

Hygenic standards for permissible levels of 1,1,2,2-tetrachloroethane in the working environment of various countries are 7 mg/m^3 in the Federal Republic of Germany, 10 mg/m^3 in the Democratic Republic of Germany and 5 mg/m^3 (maximum permissible concentration) in the USSR (U.S. EPA, 1983b).

For ingestion of 1,1,2,2-tetrachloroethane, the U.S. EPA (1980a) recommends a criterion of 1.7 µg/ℓ for drinking water. This value was based on the NCI (1978) cancer data, using the linear multistage model to estimate the level of 1,1,2,2-tetrachloroethane associated with a 10^{-5} risk of cancer.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

1,1,2,2-Tetrachloroethane is a chemical for which there is limited evidence for carcinogenicity in animals but for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIS for 1,1,2,2-tetrachloroethane.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

1,1,2,2-Tetrachloroethane is a chemical for which there is limited evidence for carcinogenicity in animals but for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIC for 1,1,2,2-tetrachloroethane.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Using the data on female mice from the NCI (1978) bioassay, U.S. EPA (1980a) derived a carcinogenic potency factor, q_1^*, of 0.20 $(mg/kg/day)^{-1}$. The data base used in the computation of this q_1^* is presented in Appendix B.

6.3.2. Inhalation. The lack of data regarding the carcinogenicity of inhaled 1,1,2,2-tetrachloroethane precludes assessment of carcinogenic risk.

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APPENDIX A

Summary Table for 1,1,2,2-Tetrachloroethane

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1*	Reference
Inhalation				ND	
Oral	female $B6C3F_1$ mice	1 µg/m³/day	hepatocellular carcinoma	0.20 $(mg/kg/day)^{-1}$	NCI, 1978; U.S. EPA, 1980a

ND = Not derived

APPENDIX B

Cancer Data Sheet for
Derivation of q_1^*

Compound: 1,1,2,2-Tetrachloroethane

Reference: NCI, 1978

Species, Strain, Sex: Mice, $B6C3F_1$, F

Body weight: 0.030 kg (measured)

Length of exposure (le) = 546 days

Length of experiment (Le) = 637 days

Lifespan of animal (L) = 637 days

Tumor site and type: liver, hepatocellular carcinoma

Route, vehicle: oral, gavage

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose (mg/kg/day)†	Incidence No. Responding/No. Tested or Examined
0	0	0/20
101	86.571	30/48
203	174.000	43/47

†Adjusted to reflect treatment on 5 days/week and exposure for 546 days of 637 day experimental period.

Unadjusted q_1^* from study = 1.5181003×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 0.20 $(mg/kg/day)^{-1}$